DEPARTMENT OF HEALTH & HUMAN SERVICES

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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1011

Research Project: Loss of Imprinting and Colorectal Cancer

Principal Investigator: Dr. Andrew Feinberg
RPN Number 99-09-07-02

Dear Dr. Dang, Dr. Klag, and Mr. Peterson:

The Office for Human Research Protections (OHRP) has reviewed your October 31, 2001 report responding to allegations of noncompliance with Department f Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46) involving the above-referenced research that were presented in OHRP's letter of August 16, 2001.

Based upon its review, OHRP makes the following determinations:

(1) HHS regulations at 45 CFR 46.116 require that an investigator shall seek informed consent only under circumstances that provide the prospective subject or the subject's legally authorized representative sufficient opportunity to consider whether or not to participate and which minimize the possibility of coercion or undue influence. OHRP finds that the informed consent process for the above-referenced research failed to meet these requirements.

Corrective action: OHRP acknowledges that the JHU IRB has required that the informed consent of subjects be obtained prior to the day of the procedure.

Action 1 - Required: By February 21, 2002, please provide a copy of the investigators revised plan to obtain informed consent for the above-referenced research.

(2) HHS regulations at 45 CFR 46.116(a)(1) require that informed consent include a description of the procedures to be followed and the identification of any procedures which are experimental. OHRP finds that the JHU IRB-approved informed consent document failed to adequately describe (a) the procedures that will be used to obtain tissue samples from the colon and (b) the nature of the DNA testing.

Corrective action: OHRP notes that the JHU IRB has re-reviewed the informed consent document and has required that the investigator revise the informed consent document to include these elements.

(3) With respect to the risks associated with the research, OHRP notes the following:

(a) The IRB-approved research protocol indicated the following:

(i) Up to "8 colonic mucosal biopsies from both the ascending and descending colon" were to be collected for research purposes.

(ii) "The primary outcome variable will be prevalence of [loss of imprinting] in colonic mucosa and blood among patients with colonoscopically normal colons as compared to patients with adenomatous colonic polyps (or colorectal cancer)." This statement appears to suggest that for some subjects the only colonic mucosal biopsies to be done would be those being done for research purposes.

(b) The IRB-approved informed consent document included no description of the risks associated with obtaining up to 8 extra colonic mucosal biopsies from the ascending and descending colon for research purposes, but simply stated that "taking these extra samples does not significantly increase the risk of colonoscopy for which you/your child is scheduled."

(c) Your October 31, 2001 report stated:

(i) "We do not believe that the consent form fails to adequately describe the biopsy procedures to be used to obtain tissue samples, as the explanation of the clinical procedure covers these procedures. We will, however, ask the investigator to add to the Risks section of the research consent form that taking research biopsies does not involve any additional risks associated with taking these research biopsies."

(ii) "We believe that there is no evidence of an increase risk of perforation and bleeding associated with cold biopsy technique done with a biopsy forceps."

HHS regulations at 45 CFR 46.116(a)(2) require that informed consent provide a description of any reasonably foreseeable risks or discomforts to the subject. OHRP finds that the IRB-approved informed consent document fails to adequately describe the risk of bleeding and perforation associated with taking eight additional colonic mucosal biopsy samples taken as part of the research. OHRP recognizes that the use of cold biopsy forceps to obtain mucosal samples presents a lower level of risk than other colonic biopsy techniques. OHRP also acknowledges that the types of risk associated with the research are no different than those associated with a standard clinical colonoscopy with colonic biopsy. However, the addition of up to eight additional biopsies of both the ascending and descending colon quantitatively increases these risks. HHS regulations at 45 CFR 46.116(a)(2) require that the informed consent provide a description of these risks. Description of these risks only in the clinical consent form was not sufficient to meet the requirements of this regulation.

(4) With respect to the level of risk for children who may be enrolled in this research, OHRP

notes the following:

(a) HHS regulations at 45 CFR 46.102(i) define *minimal risk* as the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(b) Your October 31, 2001 report stated that:

(i) The JHU IRB considered the risk category in children for the above-referenced research and determined that the research involved not greater than minimal risk as required by HHS regulations at 45 CFR 46.404.

(ii) "We submit that a colonoscopy falls into the area of routine physical test for individuals with clinical indications for the procedure."

OHRP finds that the risks associated with obtaining 8 additional biopsies for research purposes represent greater than minimal risk because (i) the cumulative nature of the exam and biopsies increases risks to the subjects; (ii) risks associated with colonoscopy are greater than those ordinarily encountered in daily life; and (iii) a colonoscopy is not ordinarily a routine physical or psychological examination or test in children or adults. Thus OHRP finds that the JHU IRB failed to satisfy the requirements of HHS regulations at 45 CFR Part 46, Subpart D for the above-referenced research.

OHRP notes that no pediatric subjects have been enrolled in the above-referenced research and that the JHU IRB has asked the investigator to determine if he wishes to recruit such subjects.

Action 2 - Required: By February 21, 2002, JHU must provide a satisfactory corrective action plan to address findings (3) and (4) above. The plan should include a revised copy of the informed consent document for the above-referenced research that includes all the elements of informed consent required at HHS regulations 45 CFR 46.116. Furthermore, if the investigators intend to enroll children in the research, please provide documentation that the IRB has adequately considered the risks involved in the research and thus satisfied the requirements of Subpart D of 45 CFR Part 46.

OHRP has the following additional question:

(5) OHRP notes that the original IRB-approved protocol for the above-referenced research

requested the use of 420 subjects to answer the research question. OHRP also notes that the list of subjects supplied with your October 31, 2001 report includes 423 subjects enrolled through July 16, 2001. Additionally, the continuing review form, received by the JHU IRB on August 2, 2001 indicated that the study had enrolled 328 subjects to date. OHRP is unclear why, if the research has already met the maximum number of subjects approved by the IRB, (i) additional subjects are being recruited for the study; (ii) continuing review is being requested without a request for use of additional subjects; and (iii) a discrepancy exists between the continuing review form and your October 31, 2001 report.

Please respond.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
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